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(54) Title: NOVEL MEDICAL USE

(57) Abstract

A method for the prophylaxis and treatment of dyspeptic symptoms using certain angiotensin II type 1 receptor antagonists and a pharmaceutical preparation comprising these compounds.

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NOVEL MEDICAL USE

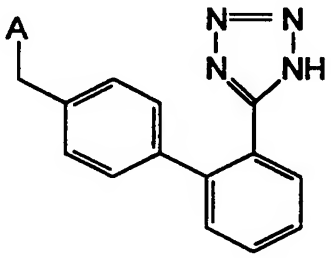
Field of the invention

The present invention is related to the use of angiotensin II type 1 receptor antagonists for the prophylaxis and/or treatment of dyspeptic symptoms and to the manufacture of pharmaceutical preparations with effects on dyspeptic symptoms.

Background of the invention

Angiotensin II type 1 receptor antagonists for which the present invention has found a new medical use are known in the art. However, nothing has been reported or is generally known concerning the pharmacological and/or therapeutic properties of these compounds with respect to effects on dyspeptic symptoms.

In connection with the present invention an angiotensin II type 1 receptor antagonist of the general formula I is employed:



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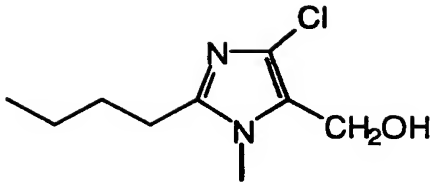

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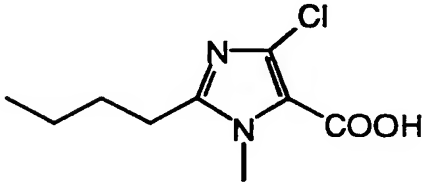

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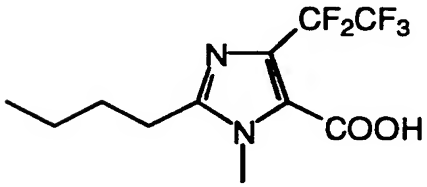

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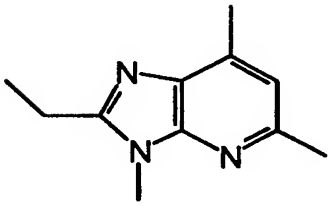

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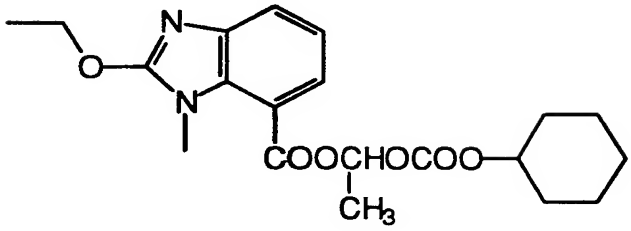

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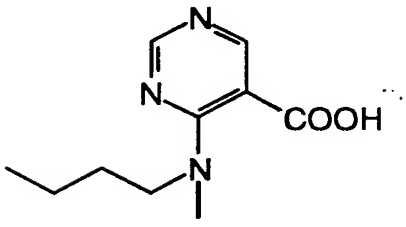

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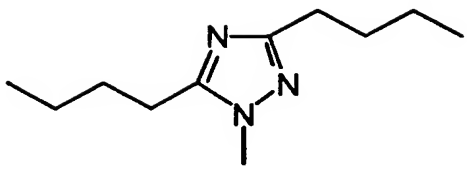

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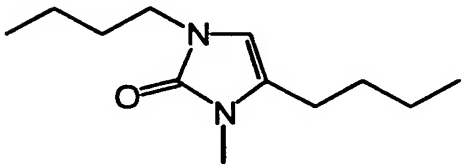

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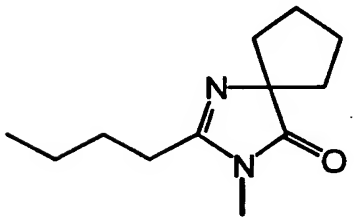

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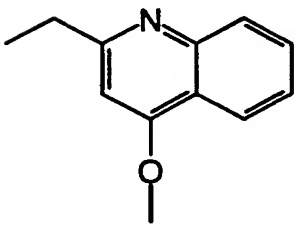

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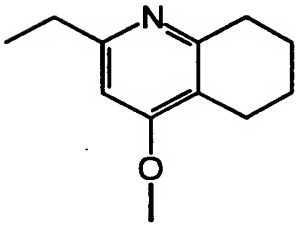

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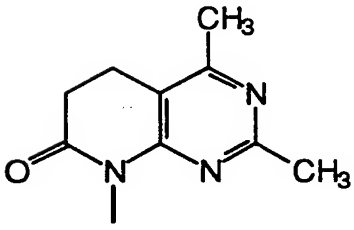

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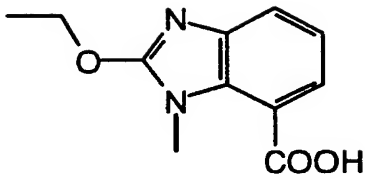

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The compounds listed above may be used in racemic form or in the form of a substantially pure enantiomer; they may be used in neutral form or in the form of a salt, preferably a physiologically acceptable salt such as sodium, potassium, ammonium, calcium or magnesium. Where applicable the compounds listed above can be used in hydrolysable ester form.

The compound of the formula I wherein A is the I:1 moiety has the generic name losartan and is known from European patent no 253 310.

The compound of the formula I wherein A is the I:5 moiety has the generic name candesartan cilexetil, code no TCV-116 and is known from EP-459 136.

The compound of the formula I wherein A is the I:9 moiety is known from under the generic name irbesartan.

The compound of the formula I wherein A is the I:13 moiety has the generic name candesartan and is known from EP-459 136.

Functional disorders of the gastrointestinal tract are common and accounts for a very large number of medical consultations. On an annual basis approximately 30% of a western population experience such dyspeptic symptoms varying from mild indigestion to severe pain. The symptomatology may be due to an organic disease (for example peptic ulcer disease) or, more commonly, be without any known origin (i.e. absence of organic pathology in the upper gut as evidenced by various diagnostic procedures). In clinical

routine the latter symptom-syndrome is commonly called "non-ulcer dyspepsia", "functional dyspepsia", "non organic dyspepsia" etc. Treatment of dyspepsia of unknown origin involves a variety of pharmacological principles (i.e. neutralization of gastric acidity, drugs affecting the motility of the gut wall etc.) some of which having doubtful efficacy and sometimes with severe side effects.

Dyspepsia due to peptic ulcers can be cured by intake of antacids and inhibitors of gastric acid secretion. Ulcer-like dyspeptic symptoms without mucosal pathology, are usually also sensitive to a similar treatment. This subpopulation of dyspeptic symptoms (acid related dyspepsia) is thus defined by the symptom-relief in association with intake of neutralizing agents or inhibition of gastric acid production by use of proton pump inhibitors or histamine type2-receptor antagonists. However the former principle is shortlasting and neutralizing drugs must thus be administered repeatedly during the day. The latter drugs have disadvantages of being expensive and exert a great impact on gut physiology as the antacid gastric conditions increase the risk for intestinal and/or systemic infections. Prokinetic drugs (such as cisapride a o) or anticholinergic compounds are other pharmaceutical principles that are utilized for dyspeptic symptoms, usually with variable effect and high frequency of side effects. It follows that available drug regimens for treating dyspeptic symptoms are impaired by serious disadvantages.

Compounds that interfere with the renin-angiotensin system (RAS) are well-known in the art and are used to treat cardiovascular diseases, particularly arterial hypertension and cardiac failure. Principally, the RAS can be interfered with by inhibition of the enzymes synthesizing angiotensins or by blocking receptors at the effector sites. Available today are renin-antagonists, inhibitors of the angiotensin converting enzyme (ACE) and angiotensinII-receptor (AII-receptor) antagonists. In addition to cardiovascular effects, some of these compounds have been claimed to excert effects on unspecified "gastrointestinal disorders".

Disclosure of the invention

The exact mechanisms behind acid related complaints form the upper gastrointestinal tract are today unknown. A prerequisite is however that luminal acid get access to the superficial mucosal cells. This is not the case during normal conditions, as a continous transport of fluid and bicarbonate provides a neutral compartment at the mucosal surface. This important acid neutralizing process is governed by a complex network of different regulatory mechanisms.

The invention describes a new method to treat dyspeptic symptoms by modulating the gastroduodenal mucosal surface-neutralizating capacity, by pharmacological interference with RAS.

Renin-angiotensin system (RAS):

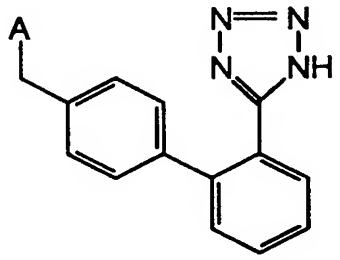
It is known that RAS, in concert with the sympathetic nervous system decreases the gastroduodenal acid neutralizating capacity. As will be clear form above, several different methods can be used in order to interfere with RAS.

It has now surprisingly been found that pharmacological blockade of specific AII type 1 receptors with angiotensin II type receptor antagonists, reversed the inhibitory effects of AII to enhancement of gastroduodenal acid neutralizing capacity. Thus, elevated plasma AII concentrations in presence of angiotensin II type 1 receptor blockade strengthens surface neutralizating capacity, in turn eliminating one prerequisite for the induction of symptoms by luminal acid.

The present application discloses that administration of specific AII type 1 receptor blockers, via an improved gastroduodenal mucosal acid neutralizating capacity, are useful in order to treat dyspeptic symptoms.

The present invention thus relates to a new method of treating dyspepsia by pharmacological interference with the renin-angiotensin system using known compounds of the general formula I above.

Thus, it has now unexpectedly been found that compounds of the general formula I



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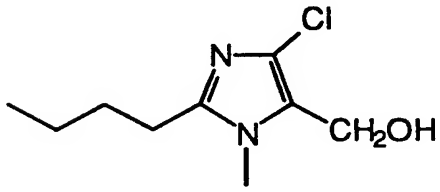

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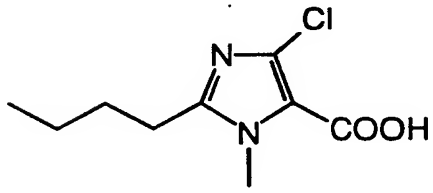

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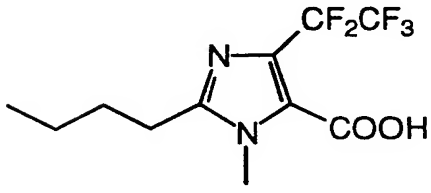

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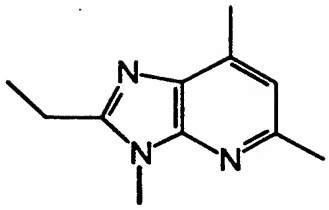

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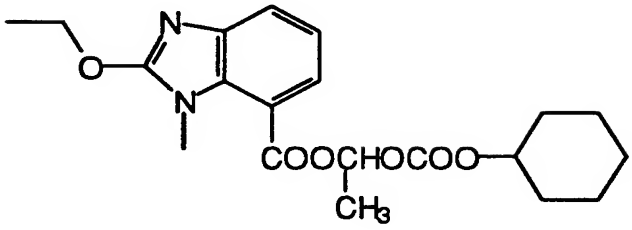

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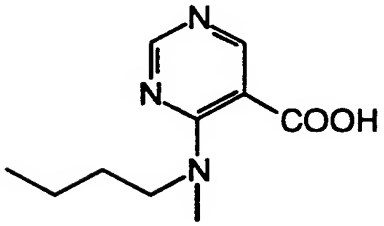

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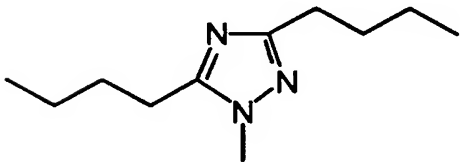

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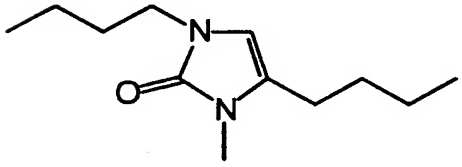

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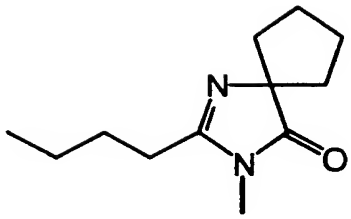

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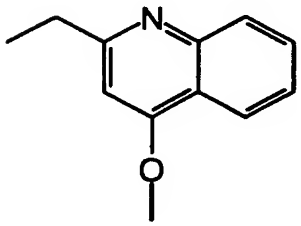

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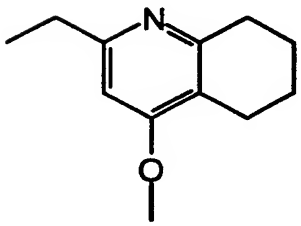

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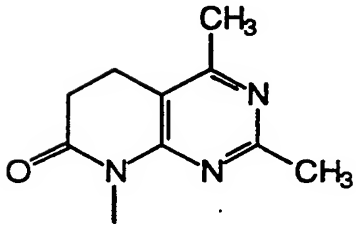

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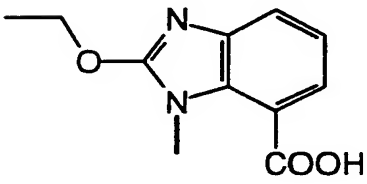

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or a physiologically acceptable salt and/or a stereochemical isomer thereof are effective in the prophylaxis and/or treatment of dyspeptic symptoms.

While the effects on gastroduodenal acid neutralizating capacity have been established in animals by the intravenous route, it is believed that the effect is a systemic effect which is not dependent on what mode of administration that is used, and accordingly the effect will be seen also with other routes of administration such as rectal or oral administration.

The dose of a compound according to formula I to be administered at prophylaxis and/or treatment of dyspeptic symptoms will vary depending on factors such as the severity of the disease and the status of the patient. The dosage range at oral, rectal as well as intravenous administration will be in the interval from 1 to 500 mg per day.

The preferred mode of the invention is the use of a compound of the formula I wherein A is I:1 (Losartan) or I:5 (T CV-116).

Scientific tests

In order to study the gastroduodenal acid neutralizating capacity, the following experiments were performed in anesthetized rats. Intravenous administration of AII in the untreated animals was followed by a slightly decreased ability to neutralize acid. In animals pretreated with the AII-receptor blocker Losartan, an enhanced acid neutralizating capacity was found in response to the same dose AII.

Table 1

Duodenal mucosal acid-neutralizing capacity in anesthetized rats before and during intravenous administration of AII.

	Untreated animals (µEq/h x cm)	Losartan-treated animals (µEq/h x cm)
Baseline	12 ±1,5	13±1,2
During AII-infusion	10±3	22±2,3 *

Data are given as means ±SEM, n=6 + 6. Significant inter-group difference (students t-test, unpaired samples) is indicated by an asterisk. Intravenous administration of AII results in an impaired acid neutralizing capacity in untreated animals. In animals, which are pretreated with the angiotensin II receptor blocking agent losartan, the same dosis of a AII significantly increases the acid neutralizing capacity of the duodenal mucosa.

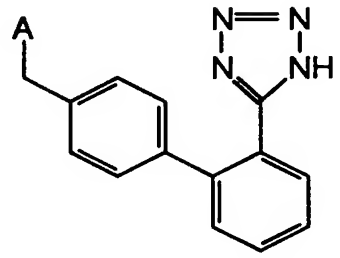
Pharmaceutical preparations

Conventional pharmaceutical preparations can be used. The pharmaceutical preparations are preferentially in the form of injection solutions, but it is also possible to use other kinds of preparation, such as oral solutions, or suspensions, tablets or capsules. Alternative routes of administrations are sublingual tablets or solutions and rectal solutions, suspensionsor or rectiols.

The pharmaceutical preparation contains between 1 mg and 500 mg of active substance, preferably 10 to 250 mg.

Claims

1. The use of a compound of the general formula I



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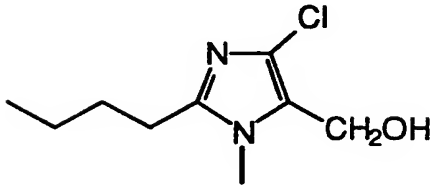

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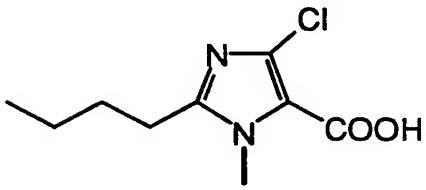

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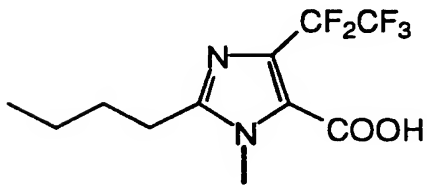

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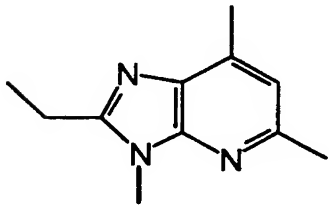

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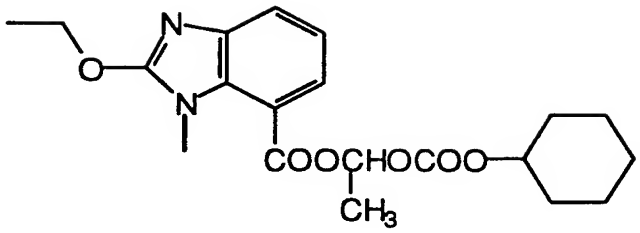

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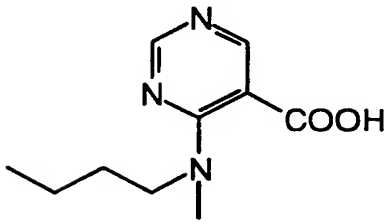

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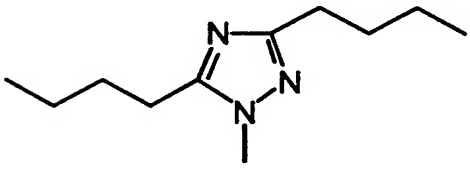

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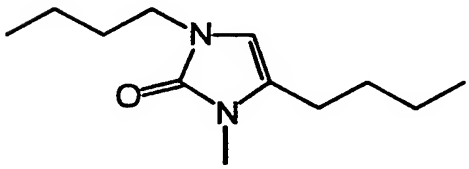

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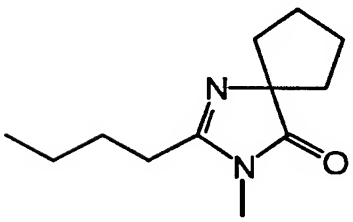
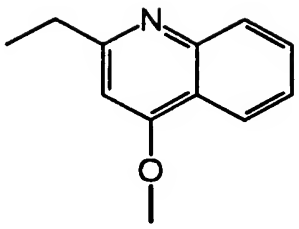
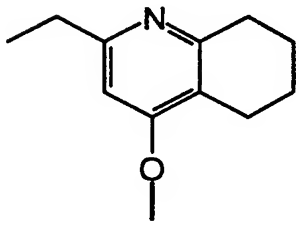


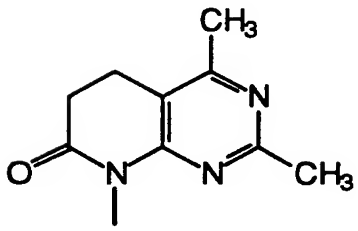
I:9



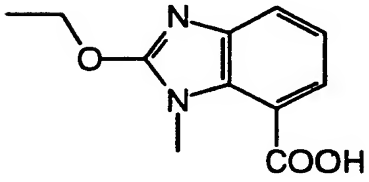
I:10



I:11



I:12



I:13

or a physiologically acceptable salt and/or a stereochemical isomer thereof for the manufacture of a medicament with effect on dyspeptic symptoms.

2. The use according to claim 1 of a compound of the formula I wherein A is I:1.

3. The use according to claim 1 of a compound of the formula I wherein A is I:5.

4. A pharmaceutical preparation for use in the propylaxis and/or treatment of dyspeptic symptoms wherein the active ingredient is a compound as defined in claim 1.

5. A pharmaceutical preparation according to claim 4 in dosage unit form.

6. A pharmaceutical preparation according to claims 4-5 comprising the active ingredients in association with a pharmaceutically acceptable carrier.

7. A pharmaceutical preparation according to claims 4-6 comprising as active ingredients a compound of the formula I wherein A is I:1.

8. A pharmaceutical preparation according to claims 4-6 comprising as active ingredients a compound of the formula I wherein A is I:5.

9. A method for the profylaxis and treatment of dyspeptic symptoms in mammals, including man, whereby an effective amount of a compound as defined in claim 1 is administered to a host in need of such profylaxis and treatment.

10. A method according to claim 9 characterized by the adminstration of a compound of the formula I wherein A is I:1 or I:5.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00758

A. CLASSIFICATION OF SUBJECT MATTER

IPC6: A61K 31/41, A61K 31/415
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC6: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CA, WPI, MEDLINE, EMBASE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	EP 0253310 A2 (E.I. DU PONT DE NEMOURS AND COMPANY), 20 January 1988 (20.01.88) --	4-8
X	EP 0459136 A1 (TAKEDA CHEMICAL INDUSTRIES, LTD), 4 December 1991 (04.12.91) --	4-8
X	GB 2263639 A (MERCK & CO INC), 4 August 1993 (04.08.93), page 6, line 1 - line 15, claims 1-8 --	1-8
X	GB 2263638 A (MERCK & CO INC), 4 August 1993 (04.08.93), page 6, line 23 - line 30, claims 1-10 --	1-8

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" erlier document but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
6 Sept 1996	19 -09- 1996
Name and mailing address of the ISA/ Swedish Patent Office Box 5055, S-102 42 STOCKHOLM Facsimile No. +46 8 666 02 86	Authorized officer Gerd Strandell Telephone No. +46 8 782 25 00

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00758

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB 2263637 A (MERCK & CO INC), 4 August 1993 (04.08.93), page 30, line 7 - page 31, line 3, claims 1-8	1-8
X	GB 2263636 A (MERCK & CO INC), 4 August 1993 (04.08.93), page 35; page 6, line 1 - line 14, claims 1-7	1-8
X	GB 2263635 A (MERCH & CO INC), 4 August 1993 (04.08.93), page 7, line 1 - line 6; page 34 - page 38, claims 1-6	1-8
X	US 5212195 A (ROBIN D. CLARK ET AL), 18 May 1993 (18.05.93), column 1, line 10 - line 19; column 1, line 35 - line 47, the claims	1-8
X	EP 0555825 A1 (DR. KARL THOMAS GMBH), 18 August 1993 (18.08.93), page 3, line 31 - line 38; page 17, line 15 - line 47, claims 1-8	1-8
A	STN International, File EMBASE, EMBASE accession no. 95266976, Byyny R.L.: "Losartan potassium lowers blood presure measured by ambulatory blood pressure monitoring", & Journal of Hypertension, Supplement, (1995) 13/1 (S29-S33)	1-8

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE 96/00758

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 9, 10
because they relate to subject matter not required to be searched by this Authority, namely:

See PCT Rule 39. 1 (iv) : Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

2. [ ] Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/96

International application No.
PCT/SE 96/00758

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
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		AT-T-	113276	15/11/94
		AU-B-	599396	19/07/90
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		CA-A-	1334092	24/01/95
		DE-D,T-	3750687	23/02/95
		ES-T-	2063734	16/01/95
		FI-B,C-	96025	15/01/96
		HK-A-	55495	21/04/95
		LU-A-	88662	01/12/95
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GB-A- 2263638	04/08/93	NONE		
GB-A- 2263637	04/08/93	NONE		
GB-A- 2263636	04/08/93	US-A-	5250558	05/10/93
GB-A- 2263635	04/08/93	NONE		

INTERNATIONAL SEARCH REPORT

Information on patent family members

31/07/96

International application No.
PCT/SE 96/00758

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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		NO-A- 944311	14/11/94
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